Toxic Interactions among Environmental Pollutants: Corroborating Laboratory Observations with Human Experience

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Combined exposures to multiple chemicals may result in interactions leading to a significant increase or decrease in the overall toxicity of the mixture compared to the summation of the toxicity of the components. A large number of chemical interactions have been described in animal studies by administering high doses of chemicals by routes and scenarios often different from anticipated human exposures. Though limited, there is some evidence for the occurrence of several supra-additive (the combined effects are greater than the simple summation of the individual effects) and infra-additive (the combined effects are smaller than the simple summation of the individual effects) chemical interactions in humans. For example, toxicokinetic interactions between several solvents have been found to occur in the workplace, whereas those involving pesticides have been reported less frequently, especially during accidental exposures. Toxic interactions involving nutritionally important metals and metalloids appear to occur more frequently, since several of them have an important role in a variety of physiological and biochemical processes. On the contrary, there is not much evidence to confirm the occurrence of toxic interactions among the commonly encountered inorganic gaseous pollutants in humans. Overall, the majority of chemical interactions observed in animal studies have neither been investigated in humans nor been extrapolated to humans based on appropriate mechanistic considerations. Future research efforts in the chemical interactions arena should address these issues by focusing on the development of mechanistically and biologically based models that allow predictions of the extent of interactions likely to be observed in humans.—Environ Health Perspect 102(Suppl 9):11–17 (1994)

Key words: toxic interactions, chemical interactions, potentiation, synergism, antagonism

Introduction

Toxic interaction refers to the qualitative and/or quantitative modification of the toxicity of one chemical by another, the process principally occurring within the organism after the exposure phase (*1*). Interactions can either result in greater-than-additive or less-than-additive toxic response. Over a thousand studies published to date report the occurrence of supra- or infra-additive toxicity from combined exposure to two chemicals (*2*). The interactive toxicity resulting from combined exposures to chemicals is a consequence of the alteration of the toxicokinetics and/or toxicodynamics of one chemical by another. Interference at the kinetic level would imply a modulation of absorption, distribution, metabolism and/or excretion of one chemical by another. Interference at the toxicodynamic level might involve a competition between two chemicals for binding to the target site or an alteration by one chemical of the susceptibility of the target cells to the effects of another agent.

Despite the report of the occurrence of several significant interactions between environmental pollutants, their relevance for humans and relative importance for regulation remain unclear and ill-defined. This situation is a consequence of the lack of chronic exposure studies with chemical mixtures and the lack of understanding of the mechanistic basis of interactions at a quantitative level. Until these issues are resolved, we probably would not be able to confidently use animal data on interactions to make quantitative predictions for humans. However, there is some direct and/or epidemiological evidence for the occurrence of several supra-additive and infra-additive chemical interactions in humans. In this article, we corroborate laboratory observations with human experience as they relate to toxic interactions among environmental pollutants and propose an approach to consider data on toxic interactions for human health risk assessment.

Toxic Interactions among Gaseous Pollutants

Interactions among gaseous air pollutants most commonly involve physicochemical mechanisms rather than toxicodynamic/kinetic interferences. A number of animal studies have suggested the occurrence of supra-additive and infra-additive interactions among gaseous pollutants (Figures 1,2). Of those interactions observed in laboratory studies, there is evidence suggesting that a few of them may have actually been experienced by humans. For example, the antagonistic interaction resulting from combined exposure to sulfur dioxide and ammoniacal compounds is thought to have been encountered during the London fog disaster of 1952 (*3*). The supra-additive toxicity resulting from combined exposures to sulfur dioxide and ozone may have been a causative factor of the high mortality of Japanese children observed in the early seventies (*4*). The reported higher incidence of cancer among workers in arsenic-smelting facilities has been explained by the supra-additive effects between arsenic and benzo[*a*]pyrene observed in laboratory animals (*5*). However, the majority of the interactions involving commonly occurring gaseous pollutants (i.e., NO_x, SO_x, ozone, aerosols) that have been well characterized in animal studies do not seem to occur in humans (*6–11*).

Toxic Interactions among Pesticidal Chemicals

Humans ingesting food preparations contaminated with one or more pesticides, workers in pesticide manufacturing and

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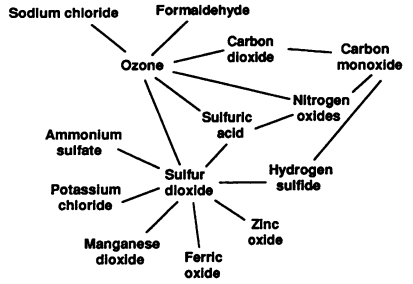

Figure 1. Supra-additive interactions among gases and particulates demonstrated in animal studies (*2*).

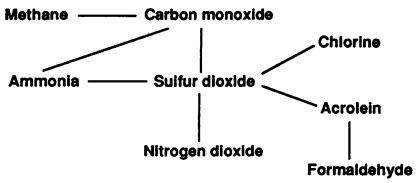

Figure 2. Infra-additive interactions among gases and particulates demonstrated in animal studies (*2*).

packaging units, and agricultural workers who prepare, mix, and apply pesticides in the fields are all potentially exposed to more than one pesticide on the same or successive days. Interactions among pesticides often involve either an induction or an inhibition of a particular metabolic pathway.

The supra-additive and infra-additive binary interactions reported among commercially important pesticidal chemicals in animal studies are summarized in Figures 3 and 4. The only instance where the occurrence of an interaction has been suspected pertains to a poisoning episode in 1976, when hundreds of Pakistani spraymen became ill following the use of a water-dispersible formulation of malathion (*12*). In this instance, isomalathion, an impurity of malathion preparation, formed in great quantities under improper storage conditions, accounted for the enhanced cholinergic effects. Animal studies have shown that isomalathion is more potent than malathion as an inhibitor of acetylcholinesterase and also potentiates malathion toxicity by interfering with the carboxylesterase pathway of malathion detoxication (*13,14*).

Toxic Interactions among Metals/Metalloids

Humans are exposed to low concentrations of several metals and metalloids arising from fossil fuel burning, vehicular exhausts, metallic ore smelting, and waste incineration. Occupational exposures may result in substantial body burden of metals depending upon the type of operation and facility. With metals and metalloids, toxicological interactions occur at both extremes of tissue exposure, i.e., deficiency and excess. This property is a consequence of several metals being required for a variety of physiological processes, e.g., as cofactors of enzymes.

The supra-additive and infra-additive interactions among metals and metalloids described in animal studies are depicted in Figures 5 and 6. Of these, the following infra-additive interactions have been investigated in humans: selenium and mercury, zinc and lead, and iron and mercury, cadmium or lead.

Selenium–induced protection of mercury toxicity in rats has been reported widely in the literature (*15–17*). There is at least one case report of beneficial effect due to selenium-mercury interaction in humans (*18*). These authors reported that allergic reactions, skin rash, incoordination and memory loss in a 39-year-old woman sensitive to mercury-based paints and sprays, were markedly reduced after she took periodic selenium supplements.

Suzuki et al. (*19*), measured the concentrations of trace elements in foodstuffs from a Japanese area with elevated intake of methyl mercury and found comparable levels of selenium as well. These authors considered that the alleviating effect of selenium is the probable reason for the toxic effects of mercury not being evident in that population. Some autopsy studies have reported that both mercury and selenium accumulated in tissues at an approximate molar ratio of 1:1 suggesting a natural protective effect by selenium of mercury toxicity (*20,21*).

Regarding the antagonistic interaction between mercury and iron, there is one corroborative accidental report (*22*). A 5-year-old boy who ingested an open battery containing iron and mercuric oxide experienced no significant uptake of mercury. This has been attributed to the reduction of HgO into insoluble elemental mercury by iron present at the gastric site.

Animal studies have indicated that supplemental uptake of iron decreases the absorption of lead, antagonizing lead-induced anemia; conversely, prevalence of iron deficiency has been associated with increasing severity of lead poisoning (*23–28*). It has therefore been suggested that the correction of iron deficiency among human populations can generally reduce lead toxicity (*29*). Interestingly, a negative correlation between blood lead levels and body burden of iron in human

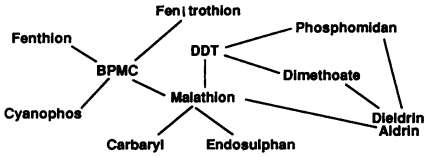

Figure 3. Supra-additive interactions among pesticides demonstrated in animal studies (*2*). Abreviations: BPMC, 2-sec-butylphenylmethylcarbamate; DDT, 1,1,1-trichloro-2,2-bis-(4-chlorophenyl) ethane.

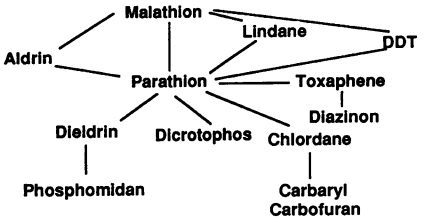

Figure 4. Infra-additive interactions among pesticides demonstrated in animal studies (*2*).

populations has been reported by several authors (*30–34*).

Similar protective effects of zinc on lead toxicity have been reported in certain animal and human studies. In a survey of industrial workers, Dukiewicz et al. (*35*) found significantly reduced excretion of aminolevulenic acid in workers exposed to both lead and zinc compared to those exposed to lead alone. Though the protective action of zinc in the case of lead poisoning is suggested (*36*), its relevance for humans still remains uncertain (*37,38*).

The absorption of zinc is reduced in the presence of inorganic iron as a result of a competition for intestinal carrier sites (*39*). According to this mechanistic description, 25 mg of total ions (as the sum of zinc and

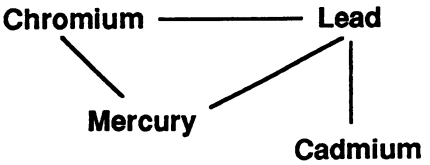

Figure 5. Supra-additive interactions among metals and metalloids demonstrated in animal studies (*2*).

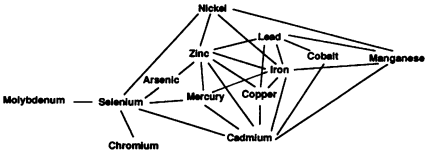

Figure 6. Infra-additive interactions among metals and metalloids demonstrated in animal studies (*2*).

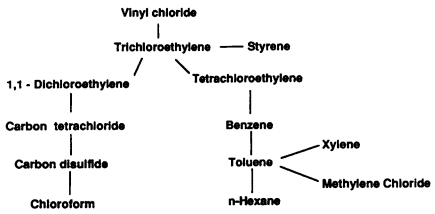

Figure 7. Infra-additive and inhibitory interactions among solvents demonstrated in animal studies (*2*).

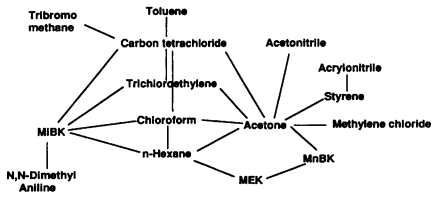

Figure 8. Supra-additive interactions among solvents demonstrated in animal studies (*2*).

iron administered orally) is the point of saturation, at which competitive effect will begin to be expressed (*39*). Evidence in support of interaction between iron and zinc/cadmium has been obtained in human studies (*40*).

Toxic Interactions among Solvents

Combined exposure to organic solvents often results in a mutual inhibition of their metabolism, since most of them appear to be metabolized by cytochrome P450 2E1 at low exposure concentrations. Figure 7 presents the inhibitory interactions among solvents determined in laboratory animal studies. Of the metabolic inhibition interactions observed in animal studies, the following have been confirmed in human volunteer/occupational exposure studies: trichloroethylene and 1,1,1-trichloroethane (*41*), benzene and toluene (*42*), ethylbenzene and *m*-xylene (*43*), xylene and toluene (*44*), trichloroethylene and tetrachloroethylene (*45*), *m*-xylene and methyl ethyl ketone (*46*) and *m*-xylene and isobutanol (*47*). These inhibitory metabolic interactions are characterized by reduced/delayed production and excretion of metabolites, and/or increased concentrations of parent chemical(s) in the blood and expired air. However, the health significance of several of these metabolic interactions has not been confirmed in workers occupationally exposed to binary solvent mixtures (*48,49*). The inhibitory metabolic interactions can be expected to result in supra-additivity with respect to the toxicity of the parent chemicals.

Supra-additive toxicity during exposure to binary mixtures of solvents has often been observed in animal studies, whenever one of the two solvents was a potent inducer of activating enzymes, or an inhibitor of detoxication enzyme system (*50,51*). Thus, most of the solvents that induce P4502E1 upon prior administration (e.g., ketones) have been shown to potentiate the toxicity of other solvents bioactivated by the same isoenzyme (Figure 8).

In human experience, isopropanol, a ketogenic chemical, was the suspect potentiator of the hepato–renal toxicity of carbon tetrachloride in two separate industrial accidents (*52,53*). Similarly, methyl ethyl ketone-induced potentiation of *n*-hexane/MnBK neurotoxicity, through the enhanced formation of 2,5-hexanedione, appears to have been responsible for the outbreak of an occupational neuropathy among the textile workers in Ohio (*54,55*) and among glue sniffers in West Berlin in the seventies (*56*).

Relevance of Animal Data on Chemical Interactions for Quantitative Risk Assessment

In evaluating the relevance of chemical interactions for regulatory purposes, it is important to consider the underlying mechanisms. Understanding the mechanistic basis enables us to determine whether or not an interaction will occur at low exposure levels in animals, and if it will occur at all in other species, especially, humans. Table 1 presents some of the mechanisms of interaction unequivocally demonstrated in animal and/or human studies.

The data generated in most interaction studies are qualitative, supporting or suggesting a specific mechanism as the possible cause of the infra- and supra-additivity. For quantitative risk assessment (QRA) purposes, we need quantitative mechanistic data on chemical interactions. For example, what is the dose–response for the induction or inhibition of metabolism of one chemical by another? What is the quantitative relationship between two chemicals competing for protein binding? Such quantitative analyses of chemical interactions can be conducted when the interrelationships among the critical determinants of chemical disposition, action and interaction are identified and integrated within a biologically based modeling framework. To date, this quantitative modeling approach has been applied only for a few binary chemical mixtures (*72*).

Since the quantitative mechanistic basis of chemical interactions has not been elucidated for majority of interacting chemical combinations, their relevance for humans cannot be evaluated confidently. On the other hand, regardless of the level of mechanistic understanding of interchemical interactions, there are instances that require the evaluation of the relevance of data on chemical interactions for specific purposes (e.g., for ensuring worker safety).

Under these circumstances, we are obliged to analyze the available data and come up with a tentative conclusion regarding the importance of an interaction for a given exposure situation. There are certain types of data which suggest that a particular interaction is unimportant for humans. These relate primarily to instances where the animal studies show the existence of thresholds for interactions which exceed the maximum allowable exposure concentrations for humans, and where animal studies confirm the occurrence of interactions which do not occur in humans exposed to low levels of both chemicals.

An example of the former case is the EPN (*O*-ethyl-*O*-4-nitrophenyl phenyl phosphonothioate) malathion potentiation. This interaction, shown to be important at high doses (*73*), was not apparent when animals were fed recommended daily tolerance levels of both chemicals (*74*), suggesting that the potentiation may not occur in humans exposed to much lower concentrations of these chemicals. Thus, Moeller and Rider (*75*), giving small oral doses of EPN and malathion in combination to human volunteers, found no evidence of EPN potentiation of malathion toxicity.

An example of the second type is the interaction among several commonly occurring air pollutants. Pulmonary biochemical and morphological changes induced by nitrogen dioxide have been reported to be enhanced by coexposure to acidic aerosols (*76*). This interaction occurs even at levels of 1 mg/m^3 of sulfuric acid aerosol and 2 ppm of nitrogen dioxide. But in human exposure studies, Stacey et al. (*7*) could not detect any synergistic effect in people exposed to low levels of both chemicals. Similarly, synergistic interaction between ozone and sulfuric acid aerosols has been demonstrated in animals exposed to atmospheric concentrations of 0.12 ppm and 5 mg/m^3, respectively (*77*). Yet, Horvath et al. (*10*) found that a 2-hr exposure to a mixture of 0.2 ppm of ozone and 1.2 to 1.6 mg/m^3 of sulfuric acid aerosol did not induce effects beyond what could be attributed to human exposure to ozone alone.

Detailed investigations of this kind have not been conducted for the majority

of the several hundred interactions reported to occur among environmental pollutants at high doses (*2*). Neither chronic animal exposure data nor human volunteer exposure data are available for these binary mixtures, rendering the assessment of their relevance for humans difficult. When confronted with a particular exposure situation involving chemical interactions, one should evaluate the available information on that interaction (or for a similar chemical combination), on the basis of factors such as dose administered and species used, to determine the relevance for humans (Figure 9). Accordingly, if such an evaluation indicates a high probability for occurrence of an interaction between two chemicals encountered in a particular workplace setting, then necessary precautions should be taken to avoid such a combined exposure. In the following paragraphs, we discuss four categories of data that should be given consideration in decreasing order of importance, while evaluating the relevance of information on chemical interactions for humans.

Interactions Demonstrated in Humans Exposed At or Below Allowable Exposure Concentrations (TLV, RfC, RfD)

Toxic interactions demonstrated in humans, in most cases, pertain to occupational exposures involving solvents more frequently than other types of contaminants. Toxicokinetic interactions among various solvents often arise from the mutual inhibition of their metabolism, thus resulting in increased blood levels. Such inhibitory metabolic interactions may

Table 1. Examples of mechanisms of toxicokinetic interactions among chemicals.

Basis of interaction	Interacting chemicals	Mechanism of interactive effects	References
Absorption			
Percutaneous	*m*-Xylene and isobutanol	Reduced absorption of both compounds due to dehydration of skin elicited by isobutanol	Rilhimaki (*47*)
	Dimethyl sulfoxide (DMSO) and pesticides	Increased dermal absorption of pesticides and other chemicals when they are mixed with DMSO, which disrupts the cellular permeability and acts as a "penetrant carrier"	Jacob et al. (*57*) Hayes and Pearce (*58*)
Pulmonary	Hydrogen cyanide (HCN) and carbon monoxide	Increased pulmonary uptake of air contaminants when they are present along with HCN, which at low concentrations increases the pulmonary ventilation rate	Dreisbach (*59*)
Gastrointestinal	Lead and iron	Decreased absorption of lead in the presence of iron due to competition for transport sites in the intestinal mucosa.	Conrad and Barton (*60*)
Distribution			
Tissue distribution	Lead and dithiocarbamates	The lipophilic lead-dithiocarbamate complex has a greater capacity than lead alone to penetrate the blood-brain barrier and causes a greater accumulation in the lipid-rich brain components.	Osakrsson (*61*)
Protein binding	Organochlorine and organophosphate pesticides	Organochlorine pesticides not only enhance the biotransformation of organophosphates, but also enhance their binding to plasma proteins and nonspecific esterases.	Trioloand Coon (*62*) Cohen and Murphy (*63*)
Metabolism			
Phase I			
Induction	Methyl *n*-butyl ketone (MnBK) and chloroform	Increased bioactivation of chloroform due to induction of hepatic microsomal P450 2E1 by MnBK.	Brady et al. (*51*)
Inhibition	Dithiocarbamates and chloroform	Decreased bioactivation of chloroform due to inhibition of hepatic microsomal enzymes by dithiocarbamates.	Gopinath and Ford (*64*)
Phase II			
Induction	Sodium sulfate and certain arylamines	Increased sulfate supply might result in a greater amount available for conjugation of xenobiotics and their metabolites.	—
Inhibition	Pentachlorophenol and arylamines	Pentachlorophenol, an inhibitor of cytosolic sulfotransferases, renders such compounds as *N*-hydroxy-2-acetylaminofluorene (that are activated by the formation of sulfate esters) less toxic.	Meerman et al. (*65,66*)
Excretion			
Pulmonary	Ethanol and mercury	Ethanol depresses the conversion of elemental mercury into ionic form. Their coexistance results in a diminution of the pulmonary retention as well as blood levels of mercury and enhances its pulmonary exhalation.	Nielsen–Kudsk (*67*) Magos et al. (*68*)
Biliary	Arsenic and selenium Mercury and selenium	Arsenic increases the clearance of selenium from the liver into the bile. Selenium, on the other hand, inhibits the biliary excretion of mercury.	Lavender and Baumann (*69*)
Urinary	Sodium bicarbonate ($NaHCO_3$) and fluoride	Alkalosis induced by $NaHCO_3$ causes a more rapid renal clearance of fluoride.	Reynolds et al. (*70*); Whitford and Pashley

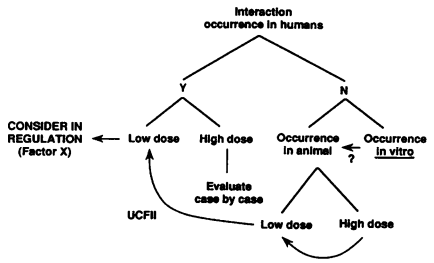

Figure 9. A preliminary schematic for considering data on chemical interactions for regulation. Abbreviations: Y, yes; N, no; UCF I/II, uncertainty factors.

eventually cause supra-additive neurotoxic effects even at exposure concentrations that do not exceed their respective TLVs. However, these toxicokinetic interactions involving mainly the biotransformation system appear to have a threshold level for each component.

Toxic interactions demonstrated in nonoccupational settings, i.e., the general environment, mainly involve nutritionally-important metals. In this regard, antagonistic effects on the absorption of toxic metals have often been reported to occur with higher intake of iron and zinc. Importantly, these interactions occur even when the dietary intake of one of these metals is insufficient, and therefore can be regarded as being more relevant for humans than most of the other chemical interactions.

Another interaction that belongs to this category is that of selenium and several carcinogens. A number of epidemiologic studies have reported an inverse relationship between the selenium status and the incidence rates of various types of cancer and cardiovascular diseases in humans (*78–80*). Recently, Yu et al. (*81*) have reported that the primary liver cancer incidence in people (in the Chinese province of Jiangsu) consuming selenium supplemented table salt was lower than that in the population not receiving selenium supplementation.

Interactions Demonstrated in Humans at High Exposure Concentrations Only

Certain chemical interactions occur only at high doses or after unusual exposure scenarios (e.g., accidental exposures). An example of this category is the ketone-haloalkane interaction. The suspected supra-additive interaction between isopropanol and carbon tetrachloride occurred in two instances, both when the environmental concentrations exceeded the allowable exposure limits (*52,53*). It is understandable that when enzyme induction is the mechanism involved, there probably is a threshold for interaction. Particularly, this type of interaction can be expected to be insignificant at low exposure concentrations, where the rate-limiting factor of metabolism is hepatic blood flow and not the capacity of the enzyme system. On the other hand, the enzyme inducers, on coexposure, may become inhibitors of metabolism of other chemicals, the importance of such an interaction being determined by the affinity and relative roles of various isoforms of P450 involved in the metabolism of both chemicals.

Interactions Demonstrated in Animal Studies at Low Doses but Potential for Occurrence in Humans Not Known

Several chemicals acting as inhibitors of hepatic and extrahepatic metabolism appear to have greater potential for interaction than inducers at low exposure concentrations. Apparently, the quantitative importance of the influence of an inhibitor on another chemical depends on the magnitude of the inhibition constant, K_i. Based on experimental and simulation studies, *trans*-1,2-dichloroethylene (DCE) has been suggested to be a potent suicide inhibitor of P450 (*82*). Therefore, metabolic inhibition of a variety of chemicals by DCE can be expected during combined exposures, even though direct evidence in humans is not yet available. Based on mechanistic considerations, uncompetitive and noncompetitive inhibitions are also quantitatively more important than competitive inhibition. Benzene–toluene interaction in animals has been described to be the result of noncompetitive interaction (*83*), indicating that this interaction can occur at low exposure concentrations. Evidence for mutual inhibitory interaction between these chemicals has actually been obtained in an occupational exposure monitoring study (*42*). Another example belonging to this category is the toxicodynamic interaction between chlordecone and carbon tetrachloride demonstrated at low doses in animal studies (*84*).

Interactions Demonstrated in Animal Studies at High Doses but Potential for Occurrence at Low Doses Not Known

Most of the chemical interaction studies conducted to date belong to this category. Typically, these studies have involved the administration of high doses of one or both chemicals by routes and scenarios often different from anticipated human exposures. The potential of these interactions to occur during low-dose, chronic exposures is not known. Consideration of the number of combinations that need to be tested at low doses in chronic experiments, by at least one exposure route, emphasizes the need to utilize alternative methodologies, particularly predictive modeling strategy. This quantitative approach involves the integration of mechanistic factors of chemical disposition, interaction, and effect into a biologically based framework, that provides the basis for predicting the extent of interactions in untested exposure situations (*72*).

There is also the possibility that an interaction, not occurring in animals at high or low doses, may in fact occur in humans exposed to low concentrations. Based on mechanistic considerations, such observations would suggest differences in the mechanistic determinants of interaction between the two species (e.g., transpecies variation in the relative roles of different P450 isozymes).

The preceding analysis of the relevance and relative importance of experimental data on chemical interactions for humans covered only certain of the important aspects. For example, the influences of exposure routes and sequence of chemical exposures in the interaction studies are not explicitly taken into account. These factors are being considered in a weight-of-evidence approach formulated by the Environmental Criteria Assessment Office of the U.S. Environmental Protection Agency (*85*).

In summary, there is some evidence for the occurrence of chemical interactions in humans, particularly in the occupational environment and during accidental exposures. We need to investigate and utilize quantitative modeling approaches in the study of interactions to uncover the animal interactions that are relevant to human exposure situations. Such a quantitative, mechanistic approach to the study of chemical interactions is fundamentally important to achieve the ultimate goal of assessing the health risks associated with human exposure to complex chemical mixtures.

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